Lactic acidosis following intentional overdose by inhalation of salmeterol and fluticasone

Alessandro Manara, MD*; Philippe Hantson, MD, PhD†; Dominique Vanpee, MD, PhD‡; Frédéric Thys, MD, PhD*

ABSTRACT

Salmeterol, a long-acting β_2-adrenergic receptor agonist used for the treatment of asthma and chronic obstructive pulmonary disease, has an adverse effects profile that is similar to that of salbutamol and other β_2-agonists. We report a sympathomimetic syndrome with metabolic acidosis and hyperlactatemia after intentional inhalation of salmeterol in a suicide attempt. A 16-year-old female patient was admitted to the emergency department approximately 2 hours after having inhaled 60 puffs of a combination of salmeterol xinafoate 25 μg and fluticasone propionate 50 μg. She presented in an anxious state with complaints of palpitations and chest pain. The electrocardiogram demonstrated sinus tachycardia and ST-segment depression in the inferior and anterolateral leads. Laboratory findings showed hypokalemia, hypophosphatemia, and lactic acidosis. Cardiac troponin I and creatine kinase MB remained within the normal range. Treatment was supportive and included intravenous fluids and cautious potassium supplementation. The next day, electrocardiographic and laboratory findings returned to normal. We hypothesize that stimulation of β_2-adrenergic receptors by inhalation of salmeterol caused this patient's lactic acidosis. This observation is consistent with the hypothesis that the hyperlactatemia observed during asthma attacks is due in part to the administration of high doses of β_2-agonists. Salmeterol overdose by inhalation appears to be sufficient to cause lactic acidosis.

RÉSUMÉ

Le salmétérol, un agent agoniste des récepteurs β_2-adrénergiques utilisé dans le traitement de l'asthme et de la bronchopneumopathie chronique obstructive, possède un profil d'effets secondaires comparable au salbutamol et aux autres agonistes β_2. Nous rapportons un syndrome sympathomimétique avec acidose métabolique et hyperlactatémie dans les suites d'un surdosage volontaire par salmétérol inhalé. Une jeune fille de 16 ans était admise aux urgences 2 heures après avoir inhalé 60 bouffées d'une combinaison de salmétérol xinafoate 25 μg et fluticasone propionate 50 μg. Elle présentait un état d'anxiété, ainsi que des palpitations et une douleur thoracique. L'électrocardiogramme montrait une tachycardie sinusale avec un sous-décalage du segment ST dans les dérivations inférieures et antéro-latérales. Les anomalies de laboratoire consistaient en une hypokaliémie, une hypophosphatémie, mais surtout en une acidose lactique. Les dosages répétés des marqueurs cardiaques (CK-MB, troponine-I) étaient dans les limites de la normale. Le traitement était purement symptomatique (remplissage vasculaire et suppléments en potassium). Le lendemain, on observait une normalisation du rythme cardiaque, de l'électrocardiogramme et des valeurs de laboratoire. Nous suggérons que la stimulation des récepteurs β_2-adrénergiques par l'inhalation de doses importantes de salmétérol peut être responsable d'une acidose lactique. Un surdosage par salmétérol en inhalation peut provoquer un syndrome sympathomimétique et une acidose lactique significative.

Keywords: hyperlactatemia, metabolic acidosis, overdose, salmeterol

Salmeterol is a selective, long-acting β_2-adrenergic receptor agonist used as a supplement to inhaled corticosteroids in the treatment of asthma and chronic obstructive pulmonary disease. The recommended salmeterol dose is 25 to 50 μg per inhalation twice a day. The effects persist for at least 12 hours. Limited data have been published on the pharmacokinetics of salmeterol. The plasma concentrations reached after inhalation of therapeutic doses of salmeterol are very low (0.1–0.2 μg/L). At higher doses, the systemic effects of salmeterol are more likely to occur, in part

From the Departments of *Emergency Medicine and †Intensive Care, Université Catholique de Louvain, Cliniques Universitaires St-Luc, Brussels, Belgium, and the Department of Emergency Medicine, Université Catholique de Louvain, Cliniques Universitaires de Mont-Godinne, Yvoir, Belgium.

Correspondence to: Dr. Alessandro Manara, Department of Emergency Medicine, Université Catholique de Louvain, Cliniques Universitaires St-Luc, avenue Hippocrate 10, 1200 Brussels, Belgium; alessandro.manara@uclouvain.be.

This article has been peer reviewed.

 CJEM 2012;14(6):378-381 DOI 10.2310/8000.2012.110581

due to a higher inhaled dose and in part due to deposition, swallowing, and absorption from the gastrointestinal tract.[1]

Hyperlactatemia with or without metabolic acidosis is a known finding during administration of β_2-adrenergic agents. It has been described during preterm labour therapy with intravenous ritodrine, during intravenous or inhaled administration of high doses of salbutamol, and in healthy volunteers undergoing intravenous infusion of salbutamol and rimiterol.[2–5] The pathogenesis of increases in serum lactate is controversial, especially in asthma attacks.[6] Transient hypoxemia, cardiovascular collapse, overloaded respiratory muscles, and hyperadrenergic state are possible explanations. We report a transient but severe uncompensated lactic acidosis with acidemia in a 16-year-old female who intentionally inhaled large doses of a combination of salmeterol and fluticasone propionate.

CASE REPORT

A 16-year-old female presented to the emergency department approximately 2 hours after reportedly inhaling 60 doses of a combination of salmeterol xinafoate 25 μg and fluticasone propionate 50 μg for self-harm. Her usual medications were montelukast 10 mg per day and salmeterol xinafoate 25 μg–fluticasone propionate 50 μg one inhalation twice a day from a plastic inhaler device (Advair Diskus). There was no past history of drug abuse. The patient was living in an adolescent treatment centre and had access only to her own asthma medications. Staff at the centre found an empty 60-dose blister pack of the salmeterol-fluticasone in her room and suspected medication abuse. The adolescent immediately admitted to overdosing on the inhaler and denied any other ingestion. According to the treatment centre staff, she was reliable.

She presented in an anxious state with complaints of palpitations and chest pain. Vital signs on presentation were blood pressure 104/43 mm Hg, heart rate 131 beats/min, respiratory rate 24 breaths/min, axillary temperature 36.8°C (98.2°F), and oxygen saturation 100% on ambient air. Her pupils were equal and normally reactive. An examination of the upper extremities revealed tremor and sweating. No heart murmurs were detected. Her systolic blood pressure monitored noninvasively up to four times an hour ranged between 97 and 113 mm Hg without signs of circulatory shock. At no point did the patient develop severe agitation, hypertonia, or seizure, nor did she require physical restraint or sedation.

The electrocardiogram (ECG) showed sinus tachycardia with a rate of 131 beats/min and ST-segment depression in leads II, III, and V2 to V6. Laboratory investigations on admission were sodium 137 mmol/L, potassium 2.6 mmol/L, chloride 104 mmol/L, bicarbonate 21.4 mmol/L, glucose 11.2 mmol/L, creatinine 81 μmol/L, phosphorus 0.64 mmol/L, aspartate transaminase 28 IU/L (local laboratory reference range 6–33 IU/L), alanine aminotransferase 19 IU/L (14–63 IU/L), total creatine kinase 291 IU/L (< 200 IU/L), MB fraction 0.2 μg/L (< 0.2 μg/L), and cardiac troponin I 0.01 μg/L (< 0.08 μg/L). There was no ketonuria. The first arterial blood gas analysis obtained 90 minutes after admission showed the following: lactate 8.3 mmol/L, pH 7.34, oxygen partial pressure (pO_2) 110 mm Hg, carbon dioxide partial pressure (pCO_2) 31 mm Hg, and base deficit 7.9 mmol/L. Serum glucose remained in the higher range, despite fasting and no intravenous glucose (Table 1).

Despite a stable clinical course, the next blood gas analysis showed a persistent lactic acidosis, with only partial compensation. The nadir pH and serum bicarbonate observed were 7.30 and 13 mmol/L, respectively, approximately 4.5 hours after presentation.

The serum toxicologic screen (by high-performance liquid chromatography, gas chromatography—flame ionization detector, and immunoassay) was negative for ethanol, barbiturates, benzodiazepines, opiates, antidepressants, salicylates, acetaminophen, and phenothiazines. Methanol, ethylene glycol, and cocaine were not tested.

There was no dysrhythmia other than sinus tachycardia on continuous monitoring, and serial measurements of cardiac troponin I and creatine kinase MB remained normal. The echocardiogram revealed normal left ventricular function (ejection fraction 66%) without valvular heart disease.

Treatment was supportive and included intravenous fluids (1 L Hartmann solution and 1 L normal saline over 16 hours) and cautious, immediate potassium supplementation (50 mmol over 16 hours). She was admitted to the observation unit. At 14 hours postpresentation, cardiac rhythm, ECG, and laboratory findings were normal. The patient was discharged 18 hours after admission after a psychiatric evaluation.

https://doi.org/10.2310/8000.2012.110581 Published online by Cambridge University Press

Table 1. Patient's blood gas levels and chemistry

Time	Sodium (mmol/L)	Potassium (mmol/L)	Chloride (mmol/L)	Bicarbonate (mmol/L)	pH	Anion gap	pCO_2 (mm Hg)	Base excess (mmol/L)	Lactate (mmol/L)	Glucose (mg/dL, mmol/L)
T0	137	2.57	104	21.4	NA	11.6	NA	NA	NA	202, 11.2
T + 1 h 27 min	139	3.4	NA	17	7.34	NA	31	−7.9	8.3	149, 8.3
T + 4 h 26 min	137	3.9	NA	13	7.30	NA	26	−12.2	8.6	145, 8.0
T + 7 h 32 min	135	4.1	NA	15	7.33	NA	29	−9.4	6.0	157, 8.7
T + 13 h	133	4.7	NA	20	7.40	NA	33	−3.6	1.2	117, 6.5
T + 15 h 30 min	140	4.23	106	21.1	NA	12.9	NA	NA	NA	NA

NA = not available; pCO_2 = carbon dioxide partial pressure.

DISCUSSION

β_2-Agonists in overdose are known to cause the sympathomimetic toxidrome characterized by tachycardia, sweating, dilated pupils, tremor, and, in severe cases, seizure, dysrhythmia, and hypotension. Typical laboratory findings during β_2-agonist overdose include hypokalemia, hypophosphatemia, hyperglycemia, and hyperlactatemia. Reported lactate levels in severe asthma attacks treated with β_2-adrenergic receptor agonists range between 4 and 14 mmol/L.[3,6,7] Hyperlactatemia is increasingly recognized to be a side effect of treatment rather than a consequence of the asthma attack.[2–11]

To the best of our knowledge, this is the first report of metabolic lactic acidosis due to an intentional overdose of salmeterol. This report is significant because the lactic acidosis developed in the absence of respiratory distress or overt metabolic disease. Fluticasone, an inhaled corticosteroid, is unlikely to be responsible for several reasons: it has not previously been reported to cause serious acute toxicity, the dose is low relative to other formulations (e.g., 500 μg of fluticasone propionate in some inhalers available in Canada), and local absorption and systemic bioavailability are reduced by the propionate ester form and by its extensive liver metabolism.[12]

One case of lactic acidosis after inhalation of salmeterol and other β_2-agents as well as crack cocaine has previously been reported, but the role of salmeterol as a single causative agent is uncertain.[11] Bustos and colleagues reported a case of lactic acidosis after inhalation of the short-acting β_2-agonist salbutamol used to treat hyperkalemia in a 14-year-old child with acute renal failure and pre-existing severe metabolic disturbances.[13]

The exact pathogenesis of hyperlactatemia during asthma attacks treated with β_2-adrenergic agonists is still controversial. Respiratory muscle failure, occult shock, significant tissue hypoxia, and impaired cardiac output are not necessarily present in these cases. Hyperlactatemia has been observed during β_2-agonist intravenous infusion in healthy volunteers and during tocolysis.[2,4,5] Both endogenous and exogenous catecholamines may contribute to the hyperlactatemia occasionally seen during acute asthma attacks, and the contribution of the treatment itself remains uncertain.[3,6,7,10]

β_2-Receptor-mediated lactate production can be explained by the stimulation of lipolysis, glycogenolysis, and gluconeogenesis, resulting in increased glucose and acetyl coenzyme A (acetyl CoA). Increased glucose metabolism leads to increased pyruvate production. In addition, the pyruvate dehydrogenase complex responsible for the transformation of pyruvate to acetyl CoA is inhibited by β_2-stimulating catecholamines and by the increased acetyl CoA concentration resulting from lipolysis. This inhibition could favour the conversion of pyruvate to lactate.[5,7,9,13]

This case supports the assertion that inhalation of high doses of β_2-agonists is sufficient for lactic acidosis in a healthy young patient without respiratory distress or comorbidities. Our patient never developed hypotension, hypoxemia, circulatory shock, seizures, or muscle hypertonia. We cannot exclude recent cocaine use, but the adolescent was under constant supervision in her treatment centre. We also cannot exclude other substances (e.g., metabolites of ethylene glycol or

https://doi.org/10.2310/8000.2012.110581 Published online by Cambridge University Press

propylene glycol) that could cause both true and false elevations of measured serum lactate. Finally, we did not obtain a simultaneous anion gap and lactate owing to infrequent measurements of the serum chloride, precluding an estimate of the delta gap during the metabolic acidosis.

CONCLUSION

Lactic acidosis may occur after inhalation of a large dose of salmeterol and fluticasone. This observation supports the hypothesis that the lactic acidosis occasionally seen during acute asthma exacerbations may be due in part to treatment with inhaled β_2-agonists such as salbutamol. The treatment of our case was primarily supportive.

Competing interests: None declared.

REFERENCES

1. Cazzola M, Testi R, Matera MG. Clinical pharmacokinetics of salmeterol. *Clin Pharmacokinet* 2002;41:19-30, doi:10.2165/00003088-200241010-00003.
2. Richards SR, Chang FE, Stempel LE. Hyperlactacidemia associated with acute ritodrine infusion. *Am J Obstet Gynecol* 1983;146:1-5.
3. Rodrigo GJ, Rodrigo C. Elevated plasma lactate level associated with high dose inhaled albuterol therapy in acute severe asthma. *Emerg Med J* 2005;22:404-8, doi:10.1136/emj.2003.012039.
4. Phillips PJ, Vedig AE, Jones PL, et al. Metabolic and cardiovascular side effects of the beta$_2$-adrenoceptor agonists salbutamol and rimiterol. *Br J Clin Pharmacol* 1980;9:483-91.
5. Tobin A, Pellizzer A, Santamaria JD. Mechanism by which systemic salbutamol increases ventilation. *Respirology* 2006;11:182-7, doi:10.1111/j.1440-1843.2006.00832.x.
6. Veenith TV, Pearce A. A case of lactic acidosis complicating assessment and management of asthma. *Int Arch Med* 2008;1:3.
7. Manthous CA. Lactic acidosis in status asthmaticus. Three cases and review of the literature. *Chest* 2001;119:1599-602, doi:10.1378/chest.119.5.1599.
8. Jee R, Brownlow H. Hyperlactaemia due to nebulised salbutamol. *Anaesthesia* 2007;62:751-2, doi:10.1111/j.1365-2044.2007.05160.x.
9. Haffner CA, Kendall MJ. Metabolic effects of beta$_2$-agonists. *J Clin Pharm Ther* 1992;17:155-64, doi:10.1111/j.1365-2710.1992.tb01285.x.
10. Creagh-Brown BC, Ball J. An under-recognized complication of treatment of acute severe asthma. *Am J Emerg Med* 2008;26:514.e1-3, doi:10.1016/j.ajem.2007.07.035.
11. Salbutamol/salmeterol: lactic acidosis (first report with salmeterol) following inhalation: 2 case reports. *Reactions Weekly* 2010;1307:40.
12. Aronson JK, editor. Corticosteroids–glucocorticoids, inhaled. In: *Meyler's side effects of drugs: the international encyclopedia of adverse drug reactions and interactions*. Oxford: Department of Primary Health Care; 2006. p. 958-77.
13. Bustos G, Ron AG, Ibarra della Rosa I, et al. Acidosis làctica secundaria a inhalacion de dosis elevadas de salbutamol. *An Pediatr (Barc)* 2008;69:577-92, doi:10.1016/S1695-4033(08)75243-3.